Assembly Line Breakdown: Protein Production Problems in Huntington's Disease

Huntington's disease slows the cell's protein factory, causing production line jams & toxicity. A faulty blueprint & missing factory assistant worsen errors. Targeting production slowdowns, not just misfolded products, may help fix the assembly line.

By Dr Sarah Hernandez | May 01, 2025 | Edited by Dr Rachel Harding

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Imagine a vast and intricate factory, humming with activity. This factory isn't manufacturing cars or electronics but rather the essential components that keep our bodies running. Inside each cell, thousands of tiny workers, known as proteins, perform highly specialized tasks. These proteins are responsible for everything from building cellular structures to sending messages and cleaning up waste. But just like any efficient factory, the cell must carefully manage its production line - ensuring that the right proteins are produced at the right time, in the right amounts, and in response to changing conditions. When this system runs smoothly, the cell thrives. When it breaks down, like in Huntington's disease (HD), problems can emerge.

Blueprints and Production Lines

Every factory needs blueprints to guide production. In the cellular factory, these blueprints are stored in DNA, the genetic material housed in the nucleus. DNA contains instructions for making proteins, but these instructions aren't directly used on the factory floor. Instead, the DNA blueprint is copied into messenger RNA (mRNA), a process akin to a worker transcribing key information onto a portable notepad.

Genetic material is like the intricate blueprint that holds the plans for every protein and cellular function that happens inside our bodies. The CAG expansion that causes Huntington's disease alters that plan.

Image credit: JESHOOTS.com

The mRNA then travels to the ribosomes - tiny molecular machines that serve as the cell's production lines. At the ribosomes, the mRNA instructions are read, and amino acids, the building blocks of proteins, are assembled in the correct order. This process, known as translation, ensures that proteins are built precisely according to their design specifications.

But just as an efficient factory must regulate how many products it produces, cells tightly control protein production to prevent waste and ensure smooth operation. In HD, a mutation in the huntingtin gene (HTT) throws a wrench into this finely tuned system, causing problems on the protein production floor.

A Flawed Instruction Manual

The HTT gene provides the instructions for making the huntingtin protein, but in people with HD, this blueprint contains a critical error: an expanded CAG repeat sequence. Normally, the HTT gene includes between 10 and 35 CAG repeats, but in HD, this number swells beyond 36, and the excess repeats create a distorted protein structure.

This flawed blueprint sets off a cascade of problems. The expanded CAG sequence results in an abnormally long polyglutamine (polyQ) stretch in the huntingtin protein. Research led by Dr. Judith Frydman from Stanford University suggests that the expanded HTT protein overwhelms the cell's quality control systems, leading to toxic interactions with other essential proteins.

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Production Line Jams

They think this happens, in part, because of a small, previously overlooked note on the blueprint of the HTT gene - a regulatory sequence called an upstream open reading frame (uORF). This uORF is like an instruction at the top of the blueprint that tells the factory workers to slow down before starting full-scale production of the HTT protein. In healthy cells, this regulation keeps HTT protein levels in check.

However, when cells experience stress, they think this regulatory note gets ignored. Instead of slowing down, ribosomes speed up HTT production, potentially worsening the disease. This work suggests that the problem isn't just the final protein product that's causing issues in the cell but also the way its production is controlled.

The real trouble begins when ribosomes hit a tricky part of theHTT blueprint - the infamous CAG repeat stretch. These repeats cause the ribosomes to stall and collide, much like a traffic jam on a production line. The more CAG repeats there are, the worse the jam gets.

This ribosome stalling may not just slow things down; it may create faulty, incomplete protein fragments that are even more prone to forming toxic clumps. The researchers used advanced techniques to track ribosome movement and found that the longer the CAG stretch, the more often these traffic jams occurred. This insight shifts the focus from the final protein clumps to the production process itself.

The Huntington's disease gene can gum up the works on the cellular factory floor, distracting other workers from doing their job, only being produced in fragments, and causing an assembly line jam. This has consequences for everything that happens after the protein is made, like many critical cellular functions.

Image credit: cottonbro studio

The Factory Assistant—eIF5A

Cells have ways to deal with these production line slowdowns. One key player is a protein called eIF5A. eIF5A acts like an assistant on the factory floor, helping ribosomes get past difficult-to-read sequences, like some that appear in the HTT gene.

But in HD, it seems that the mutant HTT protein hijacks eIF5A, pulling it away from its normal job. With less eIF5A available to guide production, ribosomes struggle even more to process HTT correctly, leading to more stalling, more fragments, and more cellular stress. The researchers found that eIF5A levels drop in HD mouse models as the disease progresses, further linking it to the problem.

The consequences of ribosome stalling and eIF5A depletion extend beyond HTT production. Ribosome collisions trigger a cellular stress response, activating systems meant to degrade defective proteins. However, when too many ribosomes stall, the system becomes overwhelmed, leading to a pileup of misfolded proteins and further cellular dysfunction. This could help explain why HD affects so many different cellular functions beyond just the presence of protein clumps.

Fixing the Factory

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Understanding how the problem starts at the production level could open new doors for treatment. The study explored whether slowing down the overall protein production process could help. They used a chemical tool to reduce the initiation of protein production, effectively easing the burden on the ribosomes. This approach reduced the formation of toxic HTT fragments, suggesting that fine-tuning protein production could be a potential therapeutic strategy.

That specific chemical tool doesn’t have good drug-like properties so isn’t suitable for clinical trials. However, it opens the door for developing treatments that would be. One approach is to develop drugs that help cells degrade toxic proteins more efficiently, preventing harmful buildup. Another strategy could involve enhancing the cell’s natural quality control mechanisms, boosting its ability to recognize and eliminate defective proteins before they cause damage.

This research challenges a long-standing focus on protein aggregates as a central problem in HD. Instead, it highlights the role of faulty protein production - ribosome stalling, translation errors, and eIF5A depletion - as possible drivers of the disease. By targeting these early steps in protein production, scientists may find new ways to intervene before the mess even starts.

This shift in focus represents a crucial step toward understanding and ultimately treating Huntington’s disease, offering hope that by fixing the factory, we can prevent an assembly line breakdown before it happens.

Sarah Hernandez is an employee of the Hereditary Disease Foundation (HDF). Authors of the work described in this article have received funding from the HDF and are members of the HDF Scientific Advisory Board. For more information about our disclosure policy see our FAQ...

GLOSSARY

huntingtin protein The protein produced by the HD gene.

PolyQ A description of HD and other diseases that are caused by abnormal expansion of stretches of DNA containing the sequence CAG repeated many times. Too many CAGs in a gene results in proteins with too many 'glutamine' building blocks, and glutamine is represented by the symbol Q.

messenger RNA A message molecule, based on DNA, used by cells as the final set of instructions for making a protein.

amino acid the building blocks that proteins are made from

CAG repeat The stretch of DNA at the beginning of the HD gene, which contains the sequence CAG repeated many times, and is abnormally long in people who will develop HD

aggregate Lumps of protein that form inside cells in Huntington's disease and some other degenerative diseases

ribosome A molecular machine that makes proteins using the genetic instructions in RNA message molecules

nucleus A part of the cell containing genes (DNA)

HTT one abbreviation for the gene that causes Huntington's disease. The same gene is also called HD and IT-15